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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,708	07/06/2001	Keith D. Allen	R-733	3959

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DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 08/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,708	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 July 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-34 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the inventions of different groups are related and would not require a separate search that is burdensome. This is not found persuasive because the inventions of Groups I-VII are patentably distinct for the reasons set forth of the record mailed on 7/30/02. A search of the subject matter of one invention would not be co-extensive with a search of the other invention, and therefore the search would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-16 and 29-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Accordingly, claims 1-10 and 17-28 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 and 17-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a transgenic non-human animal and a cell derived from said animal whose genome comprises a disruption in its endogenous intestinal alkaline phosphatase (IAP) gene, and said animal having decreased level or no IAP protein, or mutated IAP protein. The claims are further drawn to a method of making said transgenic non-human animal by homologous recombination. The specification teaches that a homozygous IAP knockout mouse exhibits the phenotype of nociceptive disorder, abnormal sensitivity to temperature, abnormal sensitivity to pain, activity disorder, and anxiety disorder (see pages 53-54).

The breadth of claims is very broad. In the instant case, the broadest claim (8) is drawn to a transgenic non-human animal containing a disrupted endogenous IAP gene. The claims encompass any transgenic non-human animal containing any type of mutation or disruption in

IAP gene regardless of the phenotype. In addition, claims 10 and 27 encompass the method of generating an IAP knockout animal using any type of recipient cell.

The amount of guidance and working example in the specification is limited. The specification does not provide an enabling disclosure to make said transgenic animal except an IAP knockout mouse. The specification also fails to teach how to use a transgenic animal with said genotype but without a particular phenotype for the disclosed utility. The phenotype of the knockout animal is the essential element that is required to practice the use of the invention (the claims must recite the phenotype). Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to make and use the transgenic animal as claimed.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous PDE7A knockout mouse. However, the claims encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a heterozygous transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. In addition, the transgene expression and the physiological consequences of transgene products are not always

accurately predicted in transgenic mouse studies (pg.62, paragraph 1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). The particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the phenotypes disclosed in the instant application is unpredictable. Thus, the specification is only enabling for a homozygous IAP knockout mouse with disclosed phenotype.

The specification fails to provide an enabling disclosure for the generation of other species of transgenic animals besides mice having a disruption in the IAP gene because the guidance offered in the specification is limited to the generation of mice harboring such mutations and no teachings or guidance are offered with regard to how one would generate any other type of animal. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell must be available to carry out the method. To date, there is no teaching from the art that homologous recombination in a somatic cell and subsequent introduction of said cell to a blastocyst would generate an offspring carrying said gene mutation. The specification does not teach such a method either. The only species in which the ES is available is the mouse (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have

been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p.1558, column 2, paragraph 1). Therefore, no knockout animals can be made for any species other than the mouse at the time of filing. As such, the invention while being enabled for a homozygous knockout mouse, generated by using ES cells, containing homozygous disruption for the IAP gene with disclosed phenotype, does not extend the predictability of the invention to other animal systems.

The specification discloses that the homozygous mutant mice display an increase in thermal sensitivity as demonstrated by decreased latency to lick their hindpaw during the hot plate test. However, the specification only provides such data for two pair of mice. Moreover, one pair of mice display very similar latency (24.68 vs 23.28) to hindpaw licking (see Table 1, last col., 5 and 6^{th} cell). It appears that this phenotype is inconsistent between two pairs of wild type and knockout mice. It is also unclear whether the hot plate test indicates thermal sensitivity, pain sensitivity and/or nociceptive sensitivity. As such, whether the IAP knockout mice exhibit the claimed phenotype of nociceptive disorder, increased pain sensitivity and increased thermal sensitivity is unpredictable.

In view of the limited guidance in the specification and the unpredictability of the art, one skilled in the art would have to engage in undue amount of experimentation overcome the problems as discussed above. Therefore, the invention is not enabled as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? Where is the screening marker located in the construct? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. Moreover, it is not clear what the word "providing" encompasses in claims 3 and 4. As such, it is unclear how the method of claim 3 differs from the method of claim 4.

Regarding claim 2, the term "screening marker" renders the claim indefinite because it is unclear what term encompasses. In other words, it is unclear how a "screening marker" differs from the "selection marker" recited in claim 1.

Regarding claims 9 and 28, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Manes et al (1990, Genomics, vol.8: 541-554).

The claims are drawn to an IAP gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in an IAP, and a method of producing a transgenic mouse comprising a disruption in an IAP gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and

int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a magnesium-dependent phosphatase gene target construct and knockout mouse.

Manes et al. teach that alkaline phosphatases are highly ubiquitous enzymes present in most species from bacteria to man, and isozymes of tissue specific alkaline phosphatases share highly homologous organization with each other (see page 541, 1st col. lines 1-3, and 2nd col., lines 12-14). Manes et al. also teach that this family of genes represent a system suitable for approaching questions concerning the evolution of tissues specific genes and their restricted expression, the mechanisms underlying genetic polymorphism, as well as the progressive change in the catalytic properties and function of enzymes in the context of an isozyme family (page 551, 2nd col., 3rd paragraph, lines 1-2 through page 552, 1st col., lines 1-5). Manes et al. further teach the cloning of mouse IAP, EAP (tissue specific alkaline phosphatase isozyme family member) gene and provided genomic sequence of these genes (see Figure 1 and 3).

Based on the teaching of Manes et al. that alkaline phosphatase gene family represents a system suitable for studying the evolution of tissue specific genes and their restricted expression, it would have been obvious to one of ordinary skill in the art to knockout the tissues specific IAP to study its function. The ordinary artisan would have been motivated to knockout the expression of the IAP gene in a mouse to study the function of this gene in context of the alkaline phosphatase family, and understanding its structure function relationship in evolutionary process, as suggested by the teaching of Manes et al. The ordinary artisan would have had reasonable expectation of success for making such a knockout mouse because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on

homologous recombination using a cloned fragment of a desired gene, and Manes et al., who teach the coding sequence of the mouse IAP gene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
August 26, 2002

DAVID GUZO
PRIMARY EXAMINER